[Slide]

As a control group--I would like to speak a little bit about our MIDCAB experience in Hanover. We have now enrolled more than 700 patients. Out of the first 500 patients we did angiographic follow-up in 6-7 percent of these patients. The first group, which was the big one with 297 patients, had a pre-discharge angiogram. What was pretty interesting was that in about 6 percent of these patients we had a highly significant problem at the site of the anastomosis, as you can see here. As a Swedish colleague presented his data with the same problem four years ago at the ASCTS and recommended just to wait because this is part of the healing response, we changed our politics, which you will see on the next slide, and just let the whole situation be as it was; waited for 3-6 months, reevaluated these patients and saw that the degree of stenosis or the number of intimal hyperplasia went down without any intervention from 6 percent to 1 percent.

[Slide]

There is another example here and, as you can see again, there is a highly significant stenosis here at the pre-discharge angiogram;

perfect anastomosis 3-6 months later when we reevaluated the patients. What we learned here is that the healing response is still evolving in the earlier time frame. We changed our angiographic follow-up from pre-discharge to a 6-month follow-up so the remaining 203 patients were evaluated 6 months after surgery instead of having a pre-discharge angiographic follow-up.

[Slide]

So, what is the Hanover experience now with anastomotic devices? Just to give you a quick overview, Hanover does approximately 2,000 open heart procedures per year. It is a large teaching institution. We are affiliated with several research centers so we are exposed to new technologies and clinical trials. The studies I have performed were with Ventrica, St. Jude and Converge. In addition, I have a little experience also with Cardica and Coalescent, however, I just want to present you the data where I have angiographic follow-up.

[Slide]

St. Jude--we had a prospective, randomized trial with 11 patients where every patient received two proximal anastomoses. One was hand-sewn and

the other one was an automatic anastomosis. This is the strongest study design that you can create. The data that we saw was that in 11 patients who were enrolled in the study and came back after 6 months and there were 10 postoperative angiograms showing that only 3 grafts were patent. We had 6 occlusions and 1 highly significant stenosis at the site of the anastomosis, with a consequent PTCA and stent after graft. Even though the patients were asymptomatic, the study was stopped because the data did not look the way we wanted to have it.

[Slide]

Even though all patients were asymptomatic, due to several reasons that we can discuss, I think independent of the cause a prospective six-month angiographic evaluation was sufficient in our study to detect performance issues of the device.

[Slide]

Ventrica was part of a multicenter trial that we did with two other centers. We enrolled 100 patients, 48 came from Hanover--

DR. TRACY: Can I ask you to start wrapping up?

PROF. KLIMA: Yes. The most important

information I want to give you here is that in the first 48 patients we had a pre-discharge angiogram and a 6-month angiogram to study efficacy of the device and performance of the anastomosis after 6 months.

[Slide]

The last study we did was with Converge. It was also a multicenter trial. We had 8 weeks of follow-up with good data. However, I think these data just showed us something about the feasibility of the device. It does not give sufficient information about how good the anastomosis will be at 6 months.

[Slide]

In conclusion, I would say that prospective, multicenter trials should be used to evaluate the performance of anastomotic devices. Retrospective clinical endpoints are not sufficient to give you any information about how good the device really is. A comparison to historical controls should be acceptable. Angiographic follow-up is the gold standard and should be used to evaluate an anastomotic device. I think, as we saw from our experience, a six-month angiographic follow-up is sufficient to address the performance

of an anastomotic device. Thank you.

DR. TRACY: Thank you. Any questions? Dr. Krucoff?

DR. KRUCOFF: Doctor, do you feel like your conclusions are equally applicable to a device used for proximal anastomosis as opposed to a device used for distal anastomosis?

PROF. KLIMA: Yes, I think so because we used this kind of protocol in proximal and distal anastomotic devices. I know there are different mechanisms causing graft failure, anastomotic failure, but the six-month follow-up is the period where I think wound healing has finished and the problems which can come up are really device related.

DR. FERGUSON: I like very much the idea that you used the patient as his own control. The question is did you have some randomized way in which it went to one vessel distally and another?

PROF. KLIMA: Yes. Either the patient needed two distal anastomoses or four distal anastomoses so that you had either a single graft with a connector or not a connector or a sequential graft with a connector or not a connector. We preoperatively randomized which graft would be

connected with the automatic connector or would have hand-sewn anastomosis.

DR. TRACY: Dr. Yancy?

DR. YANCY: Just to be clear, the limited data you showed us suggested 60 percent occlusion for the Symmetry device in the randomized effort you did. Is that correct?

PROF. KLIMA: Yes, with six occlusions out of ten patients after six months and patients were asymptomatic.

DR. YANCY: So, how has that affected your clinical use of the Symmetry device?

PROF. KLIMA: Well, after 11 patients, that was the last implant of that device.

DR. TRACY: No other questions?

[No response]

Thank you. Mr. Foley?

MR. FOLEY: Dr. Klima gave our report.

DR. TRACY: Thank you. At this point, those are all the people who had specifically requested presentations but I would like to ask the audience if there is anyone else who wishes to address the panel on today's topic or any other topic.

[No response]

We will then close the open public hearing and we will take a five-minute break.

[Brief recess]

Open Public Discussion

DR. TRACY: We will try to start the open committee discussion at this point. We would appreciate it if people who were here this morning speaking would remain for as much of the discussion as possible. Once again, thank you for being here, speakers, and please remain if it is at all possible so that the committee has a chance to ask you any additional questions we didn't get to.

At this point we will begin the open committee discussion and I would like the panel members to keep in mind the series of questions that were presented to us by the FDA earlier. So, we are trying to discuss things that will be relative to ultimately coming up with answers to these particular questions.

At this point, are there any opening questions or comments from the committee? Dr. Aziz?

DR. AZIZ: Obviously, when we talk about patency we want to get some idea of what the anastomosis is like in the OR. A number of people

are using variable Doppler flow related probes or different types to give us some idea. Then, obviously, doing angiograms a week later sometimes with those ultrasonic systems you obviously can't get an idea of the patency though you may get some idea of the flow. I mean, ideally, I think obviously one would want to know what the anastomosis looks like at the time you complete it. I believe there are some techniques afoot now that allow you to angiographically evaluate what the anastomosis looks like. Do you any of you know the device I am talking about? Are you guys aware of that? Because I think that is what should be used.

DR. TRACY: If you are going to make any comments, just come forward to the podium and please identify yourselves.

DR. WOLFE: There is an editorial--

DR. TRACY: Sir, please state your name.

DR. WOLFE: My name is Randall Wolfe. I am a cardiothoracic surgeon at the University of Cincinnati. There is published, in The Journal of Thoracic and Cardiovascular Surgery, about two years ago, an article on acute assessment for intraoperative assessment of coronary grafts. I was the author of that editorial. It outlines the

different techniques.

The newest technique, which may be the best, is a 13 MHz probe that can be placed directly over the distal anastomosis and gives data both on the flow and the anatomic construction of the graft.

DR. AZIZ: Because, I mean if there is any problem that is intraoperative, then that could be fixed there.

DR. WOLFE: That is the idea of the editorial, to ask surgeons to please do intraoperative assessment so we can remove all the technical errors.

DR. AZIZ: I mean doing an angiogram a week postop to identify the problem makes it really in a sense difficult to fix at that point. So, in our discussions I think we should really be aware of some of the newer things that are coming down the pike that would allow us to detect and correct it, if at all possible, rather than waiting for a week later.

DR. WOLFE: I would be happy to get that to you if you wish.

DR. EDMUNDS: Randy, if you are going to use ultrasound won't the clips or the metal

confound the signal?

DR. WOLFE: Actually, the answer is no. The qualification is there is some degradation of the signal if you have a complete ring but in general you can see quite well. Now, with angiography sometimes there can be a little bit with a ring right at the anastomosis but with the ultrasound you can see the anastomosis.

DR. EDMUNDS: Well, I know that when it is hand sutured. We have a paper in the Annals for that. But I thought that any time you have some metal, you know, like looking at a valve, you get reflections.

DR. WHITE: We look at stents all the time with IVIS and I think the amount of degradation can be handled. I mean, you can see the lumen pretty well.

DR. AZIZ: I think the other thing, you know, some of these, let's say, graft failures clearly are related to the site of the anastomosis but I think rheology also obviously plays a role in terms of your competitive flow in the vessel. If you are doing an LAD and the LAD is not that stenotic or appears stenotic, I mean that could be a contributing factor. Do some of these ultrasound

devices help you detect if you have competitive flow?

DR. WOLFE: Yes, the 13 MHz probe information was published. I can also provide the panel with that information if you would like because it gives you physiologic data as well as anatomic data.

DR. AZIZ: And if you detect that there is competitive flow, what then?

DR. WOLFE: In fact, there have been some studies that have shown--actually, there was a single center German study that showed that if you remove the patients that have low flow at the time of their bypass graft you can actually get a better handle on patency because those low flow grafts do have a higher incidence of occlusion in the first week.

DR. TRACY: I think there are several things if one were trying to design a trial to figure out how these things work. The immediate issue is can you put the thing on in the first place. It seems like the issue that you are addressing is assessing the acute patency issue. Maybe I could ask Dr. Emery a question. It seems as though there were a variety of technical things

that you were describing to overcome an inherent problem with the device, tacking things on, etc. Is that part of the initial assessment of acute patency? Do you look at something, do you know something by looking, and how do you pass on that type of information to another surgeon to deal with this acute issue?

DR. EMERY: We address that in several points. First of all, I think the training for the use of these devices was not adequate. It went from deploying three or four of these devices in a pig aorta with artificial pulsations to taking it to off-pump beating heart surgery which involves many other considerations. Just the difference between off-pump beating heart surgery and on-pump beating heart surgery is a whole different mental and physical attitude for the surgeon. I think my other colleagues here would agree. Then you apply a device that changes your operative protocols from distal to proximal, for instance; different ways to measure grafts and the different quality of vein grafts. So, the training I think is important.

Then, as you discover technical issues you need to carefully modify what you do to make these work, and tacking of the grafts was one thing. As

I mentioned, I over-measure the grafts specifically because I have more fear of a short graft, which is more dangerous to occlude, than a longer graft that you can lay out in various patterns. The length has very little relation to the total blood flow through the graft. It is a very minor portion of Poiseulle's equation for flow. So, you can have your graft a centimeter too long and it can be a very appropriate graft. You just have to be sure it doesn't move, flop or kink itself because the place it will kink is at the nearest fixed point, which is either the distal anastomosis or, more commonly, the proximal anastomosis. So, these little technical issues arose over using these things over time and trying to evaluate what I was doing.

DR. TRACY: Dr. Krucoff?

DR. KRUCOFF: Just scanning the questions the agency has posed to the committee, it seems to me that we are in a technology where it might be worth using stent study design from the time that plain balloon angioplasty first addressed stenting to current drug-eluting stent platforms and think about the array of technical--there are obviously some structural elements; there are technical

implantation techniques. There is a sort of acute procedural outcome; there is near-term and there is long-term outcome however we have gone about defining that over the years. It seems to me to be quite relevant to the purpose of these devices, to make the surgery faster, easier, off-pump.

You know, I think you could design a pretty clear series of targets of what are you after in using these devices and then what would demonstrate safety and efficacy along the way. The one thing that, for instance, to me seems very clear is that I do think the proximal anastomosis issues are very different than the distal anastomosis issues and to separate that would seem to me to be a very obvious place to start.

Then, getting descriptors together from the literature--you know, what is it about age, diabetes, the number of grafts, the diameter of the graft targets the surgical community has found to be predictive, published as predictive, would create a propensity population. Then, depending on what the objective of a give device is I think you could begin to draw down on when do you want to assess it; do you want to assess it; why you are doing the procedure in a way that may help you do a

better procedure. Do you want to assess it in an initial cohort where you do an angiogram before they are out of the hospital? Do you want a larger trial and get out to six months, ten months, or have a discussion about the location for the specific device what is the timing that makes the sort of best primary endpoint.

I think maybe we could find that the range of approaches here sort out into something very similar to what we have done over the past twelve years with stents.

DR. TRACY: Dr. White?

DR. WHITE: Mitch, I completely agree with you. Particularly for the proximal anastomosis issues we are talking about stent-like designs. As an angiographer, as we have just been talking about, I would also make a plea that we consider non-invasive imaging for these devices and we explore the limits of non-invasive imaging because there is a risk of angiography. There is a finite risk of angiography and if there was a way that we could satisfy ourselves about the patency and about the anatomy, morphology, then I would prefer any non-invasive tool to do this than to actually ask for routine angiography. There may not be a way to

do that. I don't know enough about the non-invasive imaging to be conclusive but that is the reason why I asked about the MR. But I think we shouldn't just sit back and say everybody has to have an angiogram at six months if we are trying to do no harm. I think if there was a non-invasive way to get that information I would like to promote that.

DR. TRACY: Of course, I agree with some non-invasive way to look at these things in the long run. I am concerned that there are different time periods. There is the acute issue where you are plugging the thing in and then how you assess that intraoperatively, then what are the time frames and what are the correct follow-ups. I think your only tool during angiography with the stents is with IVIS. Is that correct?

DR. WHITE: There are tools. There is the intracardiac echo machine that has low frequencies, 9 Hz and so forth, that is analogous to TEE in many respects, that can be used to look nicely at the ascending aorta but that is a venous invasive exam which might be preferable to an arterial invasive exam.

DR. YANCY: By the same token, you are

particularly using like a 4 tesla magnet MR and can see the proximal stenosis of grafts pretty well so you can get some structural data.

DR. TRACY: Dr. Hirshfeld?

DR. HIRSHFELD: I think I would sort of like to echo what Dr. Krucoff and Dr. White said. I think there are two core questions. The first question is do these devices confer an important advantage over traditional hand-sewn anastomoses? The second is do they have any downsides either early or late in terms of how patients are in the long term?

So, it seems to me that the way to assess these devices is a combination of documenting early patency, which I think can be done non-invasively with CT angio or MR, and then at some point documenting the morphology of these anastomoses with a technique that has high enough resolution such as selective angiography.

DR. TRACY: Dr. Mack, did you have a comment?

DR. MACK: Michael Mack. I have three comments regarding the issues that have been raised here. First of all regarding intraoperative patency, I think that is going to be extremely

problematic in terms of designing any trial. First of all, you could do intraoperative angiography. The problem with that is the image intensifiers that are available in most operating rooms, as well as the experience of most surgeons performing angiography, isn't going to make that practical.

You could do IVIS. You could do intracardiac echo or you could do epiaortic scanning. Again, the problem is you are using an unproven technique with significant user variability to prove an unproven technology and I just don't see that as being a realistic way of evaluating a new device in this situation.

Secondly, alternatives to angiography after surgery for follow-up, we have experience with both MRI and EBCT. EBCT is great to show whether the graft is occluded or not occluded but it is not accurate in terms of degree of stenosis, which I think is a harbinger in these grafts of potential occlusion later on so it will not pick that up.

MRI, at least with stents in our experience and I assume you could make the jump to anastomotic connectors, creates a flow void in the area where the stent is and you cannot diagnose

instant restenosis with cardiac MRI.

Thirdly, I think what a real problem of this whole trial design is, is that there are a number of devices out there that have been given previous guidance as to this was a 510(k) pathway and that six-month angiographic follow-up would be an appropriate endpoint to determine safety and efficacy. I realize that the function of this panel, first and foremost, is patient safety and secondly efficacy, but there are a whole number of studies that are out there done that have six-month angiographic follow-up and a very real, practical question is what happens to those studies and what happens to those devices? Do they just get thrown away and we start all over again?

I would say that if that is the case, I think that a number of these devices will never make it to market and the companies will go under. I realize that that is not your purview but I think it is a very practical consideration of the problem that exists right now. Thank you.

DR. TRACY: Dr. Zuckerman?

DR. ZUCKERMAN: Dr. Mack has raised some important points. I would indicate to both the industry and the investigators here that the

ongoing studies are developing important data sets for FDA. The question that may need to be raised for some of these companies that are in the process of doing these studies is, depending on what advice this panel gives us today in addition to what is ongoing now, what might be additionally required. But the agency is by no means saying that what companies and investigators have performed to date needs to be thrown out.

DR. TRACY: Dr. Kato?

DR. KATO: I have a question for Dr. Martin. Can you comment a little bit about the time frame of when you performed your catheterizations in terms of whether 6 months or 12 months, in your experience, was of any value or do you have to take this out further in your experience?

DR. MARTIN: Well, I will be honest with you, most of my presentation was obviously anecdotal based on the one patient I saw. My problem is the fact that you are subjecting patients to a metallic device without the benefit of platelet inhibition. We know with recent FDA warnings about subacute thrombosis in drug-eluting stents how important that is, and these are

patients that don't get Plavix usually intraoperatively because of the bleeding consequences, or may not get it for 48 hours because of the absorption issues.

So, the damage is already done when you install these devices. Basically, the platelet adhesion and the basis or the nidus for fibril intimal hyperproliferation starts immediately and that is exactly what I postulated when I saw this first patient, first case. Basically, that is what I think the problem is. I mean, you can't put metallic devices in an aorta. Like Dr. Weinberger said, it is a different pathology virtually.

But the point is you are trying to auger a hole, start some sort of clotting cascade with your thumb while you are getting this device ready to implant so you are hoping it clots, but then you don't have anything on board to keep it from over-clotting for instance. I think some of the early cases that had thromboses of the grafts were related to that and I think the nidus begins at the time of implantation with these devices, period, because they are metallic.

Now, as far as my experience, I have a very low threshold for cath'g these patients. I

mean, basically anginal syndromes, thallium--yes, we are trying to get all these patients back. The problem is that a lot of these patients are taken care by a multitude of cardiologists and, you know, they each have their own individual thresholds for doing non-invasive testing, for instance, in bringing the patients in and, of course, economic considerations as well.

But, I mean, my opinion is the same as it was two years ago and now--as I was talking to Dr. White--what do we do with these patients? Can we use drug-eluting stents? Well, not really because a lot of these patients, as was shown in the article two months ago in JAC by Cavendish's group, have a high propensity for restenosis because of the propensity that we see in a lot of stent patients for instant restenosis.

So, I hope I have answered your question but the bottom line is I think the injury starts at the time of surgery whether technical or not technical. Every film I looked at on the screen showed evidence of proximal hyperproliferation or intimal endothelial proliferation, every one of them, every graft that was shown up there, and I think that is part and parcel of this whole

problem.

DR. KATO: Well, my question was really in your experience is it going to be 6 or 12 months for your study.

DR. MARTIN: That is a great question but basically we normally treadmill people within six months, use thallium treadmills. Normally most of them are cath'd within six months. That is when we use sort of a definitive marker. But, as I said before, there are lots of patients that can't get back for various reasons and there are patients that have to be done over and over again. Some of these patients have been done six, seven and eight times in various circumstances.

DR. TRACY: Dr. Bridges?

DR. BRIDGES: I have a question for anyone either on the panel or in the audience. Do we have six-month angiographic data on the Symmetry device? Because one of the key questions here is what is the length of time that it takes to discover a problem with these devices. Is that data available because I haven't seen it published and I was wondering if anyone can comment on that.

DR. SLAUGHTER: Mark Slaughter. I can't specifically answer for Symmetry; I think I know

the answer. But I would like to respectfully disagree with Dr. Martin so it doesn't go unspoken. To say, you know, a stent is a stent and metal is metal and these things are all the same is not true. And, there is lots of data for the distal anastomosis and Converge. They do get Plavix starting within 24-48 hours. And, the German experience which he put up is 60 days and they have 100 percent angiographic follow-up and it is 97 percent patency, and they have morphology. That is, there is no stenosis; there is no narrowing.

So, to say that because you have something in the lumen and you didn't have Plavix automatically means it has to fail is not true. Within our own experience with now half of our patients back and angiograms 6-7 months, we have no occlusions and we have essentially no stenosis whatsoever. So, to just sort of blanketly say that without, you know, preoperative medical therapy if you have this foreign body it automatically means failures and it will never work is not true.

By the same token, there are issues related to that as to material design, where it is placed, and what type of injury occurs are important issues and need to be answered along the

way. I think the issue of six months, I mean, I think someone needs to step up and answer but the idea is in any other study so far with these devices at six months the majority of all failures are identified, or you have changes in morphology that would subsequently predict later failure.

DR. EDMUNDS: To answer your question, Charles, blood never sees the metal. It sees a granular layer of proteins that are adsorbed onto the metal or any foreign body and that is what the reaction is. The mosaic of those proteins is empirically derived but it never sees the metal.

DR. TRACY: Prof. Klima?

PROF. KLIMA: Uwe Klima, Hanover. As I presented in my talk, yes, we have postop follow-up, angiographic follow-up with the Symmetry device six months after surgery and this was sufficient enough to detect a real, real problem at the site of the anastomosis even those these patients were asymptomatic. I think this is a very clear message to say that even though you have asymptomatic patients you might have a significant problem at the site of the anastomosis and I think the six-month interval from surgery until you put the patient back into a cath is sufficient to

detect any significant problem at the site of the anastomosis.

DR. TRACY: Dr. Zuckerman?

DR. ZUCKERMAN: Although you have reported very important six-month angiographic follow-up results, what percent of your cohort had six-month angiography?

PROF. KLIMA: My total cohort?

DR. ZUCKERMAN: Yes.

PROF. KLIMA: Well, 67 percent of our MIDCAB patients, 100 percent of the Ventrica patients, 100 percent of the Converge patients and 100 percent of the St. Jude patients.

DR. ZUCKERMAN: Right, and so in terms of this advisory panel appreciating some of the problems that we have and whether six months can be the gold standard, our paradigm has usually been at least about 80 percent angiographic follow-up, assessed in an independent core lab, to really make statements about the totality of the data. So, I would ask people to consider Dr. Bridges' question. Even if certain data have been spoken of here, has the angiographic follow-up been sufficient or is there still a paucity of data, reviewed independently, to make any decision regarding Dr.

Bridges' question about what is the length of follow-up.

DR. TRACY: Could I ask you, did you have other assessments on those patients, other non-invasive assessments performed before the angiogram or was this just part of the routine follow-up?

PROF. KLIMA: Well, intraoperatively we did an ECHO measurement of flow. However, I am not a big believer about the accuracy of how good the ECHO is. It gives information about is the graft patent or is it not patent but it does not give you very good information about is there 50 percent stenosis, yes or no. If we have a situation where we see that there is no flow in the graft by ultrasound, yes, we go back and we do anastomosis again. All the other information you get is yes or no; it is patent or it is not patent, no more than this.

DR. WHITE: She was asking about thallium stress tests. Did they detect your asymptomatic occlusions? Did any other non-invasive functional tests detect asymptomatic occlusions?

PROF. KLIMA: Well, there was a clinical interview, so to say, when we brought the patients

back about how they would perform. We put them on an exercise stress test and about half of the patients showed ischemia when they were on the bicycle, so to say. But in the clinical situation of daily living--you know, how patients move, whatever they do, they were asymptomatic.

DR. WHITE: So, the important data then is that the non-invasive test for ischemia did not completely identify the set of patients who had occlusions.

PROF. KLIMA: Exactly. That is why I would really recommend to you to have a six-month angiographic follow-up and if your data look very good I think you can go on with the clinical tests a year later, bring back the patients and see how your patients are doing. In case they are having troubles you certainly have to reevaluate those patients. Either you do it with an angiogram, which I would not do because the angiogram itself has some morbidity, so to say, or some problems coming up sometimes with an angiogram. I think valuable information would also be with an MRI or CT scan.

DR. TRACY: Dr. Hirshfeld?

DR. HIRSHFELD: I wanted to ask Dr. Emery,

because Dr. Emery spoke quite a bit about the technical aspects of using these devices, we have heard reports from a couple of groups of very experienced surgeons and they believe that they have an excessive device failure rate. You have obviously great experience using this device and I wondered if you could offer an opinion as to whether or not the excessive device failure rates may be attributable to technical considerations in terms of how the device is used, and how you would distinguish between that an inherent characteristics of the device.

DR. EMERY: I was just thinking that our experience is very much different from Dr. Schoettle's and I would like to get together with him actually and see our differences. On the angiograms, I just reviewed them and there are two out of all the ones I showed. Dr. Martin had had a proximal stenosis; the others were widely open proximally.

One of the issues that Ms. Marders dealt with was the dehiscence which was a disastrous event. I think that is a technical problem because the graft is too short and when the patient's heart fills or they cough or retch after surgery, they

can pull on that device and pull it off. It is clearly not as strong a suture or as strong as the device Dr. Hausen described. So, I think you need to establish some in vitro criteria for these valves before implantation, not just animal data but the parameters of their strength, just like you proposed for cardiac valve prostheses before they go into clinical trials. I do think the technical issues need to be dealt with because there is no data as to what surgical techniques contribute to failure and that certainly could be one reason, plus regional differences in patient characteristics. It is clear that there are differences in our regional populations--incidence of diabetes, obesity, male versus female, quality of the veins, these issues all come up and these are not addressed in any of the trials that were presented, except for Dr. Mack's trial which came out with diabetes as a very important issue in these device failures.

DR. WHITE: Are you still using this device?

DR. EMERY: I do for specific indications, people over 80 and in people that have evidence of calcified aorta. Dr. Jim Harte's series is a big

proponent for epiaortic scanning before coronary surgery. If people have aortic disease, then I will use it. I do not use the smaller size unless it is absolutely necessary for very specific and patient-oriented reasons. It has its indications and contraindications I think, like we try and do with all of our procedures, processes and medication in the field of medicine.

DR. TRACY: Dr. Krucoff?

DR. KRUCOFF: I just wanted to step back to the notion that the range of devices we are talking about, in addition to their individual differences, extend from some that are approved and on the market, some that are already in the course of clinical trials that were discussed and designed, and then others that I guess are thinking about the future. It seems to me there are some common pieces that we could focus on them.

One of them is called informed consent. I think whether a trial is being planned or is already in motion or whether a surgeon is planning to use a device that is on the market in a human being, we could look at the informed consent document and process across the board and make sure that it contains the appropriate information

reflecting current knowledge about the potential risks or benefits.

The other is medication. I think there is no question that while maybe loading people with Plavix preoperatively has some downsides, once a gadget like these goes in and hemorrhage and other circumstances is not an issue, anti-platelet therapy across the board, whether you are already doing a trial, is worth probably making sure that you can do as well as possible.

Lastly, in the safety assessment is the use of a data and safety monitoring board. What we again very directly from the stenting world recognize is that angiographically, whatever your time window is, you are going to generate clinical events because if at six months people aren't symptomatic but you see 90 percent stenosis, the tendency to do something about that is going to impact the population.

So, at least insofar as, for instance, with a good data and safety monitoring board supervision program you could move the angiographic endpoint to a later point and if you have a trial that has done all the paperwork but hasn't enrolled a patient it may be a little different than a trial

that has enrolled 210 out of your 215 planned patients. But I think for anything that is in motion, recognizing that an angiographic endpoint--and is pretty clear from what we have heard that detailed morphology of how these things heal is probably going to be an angiographic endpoint somewhere along the line. But if we push that time window later clinical events will occur more consistently with the natural history of the intervention and be less driven by a response to an angiogram.

So, I think as long as there is a safety board or there is a safety surveillance mechanism that can make sure patients aren't being harmed, there is a way to envision using angiographic endpoint but pushing out later to allow clinical events to also tell you how patients really respond to these devices.

I think from consent to data safety and where you put your time window, frankly, whether it is for a device that is approved and on the market or for a trial that is already enrolling or for a trial that is being planned, that will at least give a backbone that we have learned a lot with stent-like devices that you could think about

structuring trials.

DR. TRACY: Dr. Edmunds?

DR. EDMUNDS: Bob Emery, is it your feeling that the technical limitations of the anastomotic device are much more constrained than they are with the hand-sutured anastomosis proximal, one question; distal for the second? And we are talking just vein grafts.

DR. EMERY: Not necessarily, Dr. Edmunds. I think, like anything, we have to learn how to do it and I am sure my first few proximal anastomoses when I was a cardiac surgical fellow were not as good as they are right now after twenty years. I think the same is true with the devices and there may be a need for more mentoring on the first several cases so someone can suggest what is good and what is bad, much as is done with other more complex devices. These devices seem intuitively simple but obviously we are coming to the conclusion here that they are not intuitively simple. They have a lot of subtleties in their use both in terms of healing, deployment and events that occur, and those all need to be addressed, not just the fact that you push a button and you have an anastomosis. That is clearly very simple.

These things, like any other techniques in our medical profession, we need to learn how to do them.

DR. EDMUNDS: But you showed us angiograms in which there were problems, that you needed to put it on the side of the aorta towards the pulmonary artery, which you don't need to do for hand-sewn anastomoses. It has to be totally at right angles. It can't be at a little bit of a hood. Those are the constraints that seem to be much more confining than would be in a hand-done anastomosis. Is that true or not true?

DR. EMERY: Yes, and they have to be defined. That is what I was talking about for some of the in vitro tests and even the in vivo tests before the application to our clinical patients. It is not just patency that is important; it is how you use it and define the limitations of the device as part of the preclinical issues that go into preparation for a clinical trial.

DR. EDMUNDS: Therefore, the device anastomosis is less robust than is a hand-sutured anastomosis. It is less tolerant of small error.

DR. EMERY: That is possible. You know, it is possible but, on the other hand, sewing an

anastomosis in a diseased aorta is less tolerated by the patient and there is value in these devices even though they may be more complex. Also, on one angiogram I showed side-by-side anastomoses where one was hand-sewn because I was over-aggressive in pulling the vein graft and pulled the connector right off the aorta, which, you know, caused a little bit of a stir in the operating room, of course. The other connector was just fine so I just hand-sewed the other anastomosis. The patient returned at three months with both occluded. I can't explain why there was a difference in something like that occurring.

DR. TRACY: Dr. Yancy, then Dr. Weinberger, Dr. Kato and then lunch.

DR. YANCY: Putting some thought into a clinical trial design and thinking of endpoints that would be evaluated in that design, I have not heard a discussion this morning about the presumed advantages for this device, specifically the time of the proximal anastomosis, decreasing that variable to the extent that that is clinically relevant. The second would be the CNS event circumstances because that was purportedly one of the major reasons for developing the technology.

Are we to assume that that has been proven or are those issues? Because in my judgment, if we are addressing questions of efficacy with regards to the integrity of coronary perfusion and we have missed the purported benefit, then I think there are some serious questions that have to be addressed that are more global than trial design. Are there people in the audience that can specifically comment on the CNS issues and the timing issues, especially if we follow the most recent discussion that more care and consideration needs to be made in generating these proximal anastomoses?

DR. BRIDGES: I don't think there is any data other than speculation that I am aware of, unless somebody else knows otherwise, that prove those points that you made. I mean, I think the supposition is that there would be less incidence of stroke and that may very well be true but I don't think that that data is available.

DR. YANCY: Well, I respect that but there is a comment in our packet that 30,000 of these devices have been implanted and we have any number of events reported to the FDA, and I think if we are dealing with supposition and speculation the

trial design needs to be a bit more rigorous than we may have thought earlier today.

DR. FERGUSON: Can I respond to that?

DR. TRACY: Yes.

DR. FERGUSON: I think you are mixing a little bit apples and oranges because the genesis for many of these mechanical devices has been MIDCAB and off-pump where putting on an anastomosis by hand is much more difficult, sometimes impossible. It obviates the use of an aortic clamp which is not possible if you are doing it hand-sewn. So, I think that responds to the issue of CNS issues because those issues are due to clamping the aorta so you can do the anastomosis of the hand-sewn.

DR. AZIZ: But then they should be able to look at the cases they have done and see what the incidence of neurological problems is in the 30,000 cases or so that have been mentioned. Theoretically, it should be less than what was expected. I mean, somebody should have that data.

DR. TRACY: Dr. Weinberger?

DR. WEINBERGER: I would like to sort of echo and expand a little bit on what Dr. Krucoff said. I think that in the past couple of years the

FDA, together with the cardiology community, has developed a paradigm for analyzing new endovascular stents. If you go back to 2000 or 2001 in the early days of drug-eluted stents, the studies that were designed included both clinical endpoints and angiographic substudies, and the angiographic substudies were done to power angiographic endpoints which are completely different than powering clinical endpoints.

I think that both are important. I think the surgeons and a lot of us are focusing on morphological endpoints right now, and I think the study done to get a morphological endpoint when you have a continuous variable could be done with a much smaller number of patients.

On the other hand, the FDA standard in the past has always been clinical benefit to patients or at least clinical equivalence to previous devices and I think we need to gather clinical endpoints for those particular pieces of information. So, what we really need is to define what the rates of major adverse cardiac events are in hand-sewn saphenous vein surgery at one year or two years, some time point, and use a clinical endpoint for that piece of the information.

We are all sort of focusing on an angiographic endpoint which, at best, is going to be a surrogate to suggest what is going to be happening clinically and probably should represent only a substudy of an ultimate study that is done to approve this.

Now, I am sure that the manufacturers are going to howl and say that we are really subjecting this to PMA standards, but I think that given where we are and the fact that we have introduced what appears to be problems at unexpectedly high frequency the data necessary to at least inform patients that we are not exceeding the previous event rates are necessary.

DR. TRACY: Dr. Kato and then we should really break for lunch.

DR. KATO: Why don't I let Dr. Frater talk and I can reserve my comments until after lunch.

DR. TRACY: That is fine.

DR. FRATER: I just want to try to respond to a couple of the issues that were raised. You did raise the question of angiographic evidence at 6 months on the connector in a miscellaneous group of patients in which angiograms were available. There were 221 of them. The occlusion rate between

6-12 months was 20 percent. The range was 2.3 percent to 58.3 percent. That is one of our problems, dealing with a range that wide. How can you possibly account for it?

It is perhaps fair just to mention that there are studies already published in abstract form in which the outcomes judged by MACE followed by angiography are nowhere near what you heard this morning. I will just quote one from Brady, University of East Carolina, with 400 patients with 650 veins and they found, based on clinical events, 3 veins that had problems of occlusion or stenosis. The difference between these various studies is enormous.

In terms of neurological episodes, those 400 patients studied from 2001 to September 2003 had a 1.7 incidence of neurological adverse events in the postoperative period. Dr. Schoettle could tell you about his connector patients and their CNS adverse events but I will leave him to do that if he wishes.

So, I won't spend more time; we clearly don't have time, but there are other similar good series to report that we are faced with extraordinary diversity in results from competent

people.

DR. TRACY: Thank you. Why don't we break for lunch and let's be back here at 1:20.

[Whereupon, at 12:20 p.m., the proceedings were recessed for lunch, to reconvene at 1:20 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. TRACY: If everybody would please take their seats, I would like to resume the open committee discussion because I know there are a lot of additional issues that need to be addressed this afternoon.

Again, I would like to thank presenters for hanging around to help us clarify some issues. It is very helpful to get the input of everybody who has made the time to come here. This is a difficult issue that we are wrestling with because there are an awful lot of variables that are involved in the discussion that we are here to have. At the end of the day we are expected to be able to answer some questions or begin to answer questions that have been posed to us from the FDA.

I would just like to at this point sort of summarize what I see as some of the complexities that we are looking at right now. I think there is a variety of variable here that we are discussing. One is what type of devices are we talking about. There is a variety of devices that are out there and there is a variety of devices that are coming down the pike.

I think an issue that we have to address

is, is the analysis of each of these different types of devices going to be the same. My suspicion is that that will not be true but is there some sort of paradigm we can come up with that would help to analyze what type of process should be gone through to look at different types of anastomotic devices?

I think one thing that is clear that we have heard so far today is that the target vessel is very important--whether something is being connected to an LAD, whether it is an aortic anastomosis or artery or vein anastomosis. these are variables that are inherent in this type of device and the analysis or process to look at these things may be different if we are talking about distal or proximal anastomosis, and how do we handle that in a given patient population?

I think we have heard an awful lot about operative variables, some of which may be technically overcomable, some of which may not be. Maybe a MIDCAB is very different from a coronary bypass graft placed through a thoracotomy. How do we handle that?

So, let's focus on some of those things as we think about our trial designs and what

parameters we can look at both acutely, what is the appropriate mid-term analysis on these patients, and what does long-term analysis and long-term follow-up really mean. Are we looking at an anatomic outcome or are we looking at a functional outcome? And what other outcomes are appropriate to consider?

One of the original reasons perhaps for developing any of these anastomotic devices was to avoid some of the neurologic outcomes that come from cross-clamping the aorta. So, what other outcomes do we need? We sort of focused on angiographic but are there other neurologic or other types of outcomes we need to think about?

The final area that I would like people to sort of focus in on is that it does seem to be almost a separate cardiovascular surgeon training program to learn how to use these things, and what is it that needs to be done to train appropriately for the use of these devices?

So, if you can try to keep in the back of your mind the questions that have been posed to us and let's try and focus our way through some of these issues.

DR. KRUCOFF: As a point of order, I don't

know if this is inappropriate or appropriate but would it be possible to actually go through the afternoon discussion by starting with the questions instead of doing the discussion and then ending with the questions? We are not voting.

DR. TRACY: We can do that but I think there may be some additional issues. You have the questions listed here so if there are additional things that you think are relevant before we answer the questions, I want to give plenty of time for discussion and input from the audience on this. Yes?

DR. MACK: Michael Mack. Do you want me to start? DR. TRACY: Sure.

DR. MACK: I have a couple of comments based upon what you just said. The first alludes to what you said, you need a whole separate training program to implant these devices, and a lot of attention was focused on Bob Emery's presentation about the permutations that are necessary for this. I think this addresses the issue that implantation of a medical device by surgery or by a catheter is not a pill and you don't just give a pill and a placebo and that is the variable. There are intricacies associated

with the implantation of a device. It is not that the use of an anastomotic device is necessarily more constraining or that the margin of error is narrower, but it is just different and just because you have been sewing coronaries for twenty years doesn't mean you can automatically put in a device the first time.

I will go to the analogy of drug-eluting stent devices. There are a whole bunch of adverse events with subacute thromboses that happen immediately upon approval of this. It probably had to do with the fact that it is a device, a particular type of stent that most cardiologists weren't implanting. It was just different. It is stiffer. The delivery platform wasn't as usable. How high do you inflate the balloon? Do you overlap stents? What is the amount of coverage that you have? All those little intricacies just had to be brought up to speed and were different than cardiologists had been doing before.

It is the same thing with anastomotic devices. you find out that you have to put a suture to tack a vein graft to keep it straight coming off, whereas you don't with a sutured one, and there are little permutations like that that

you find when there is broader experience with it.

The second has to do--it was either Chris or Clyde that mentioned this, we talked a lot about adverse events about the procedure. Well, what about the benefit? Well, I think there is benefit potentially both with the device itself but what it is ultimately going to lead to.

One is the device itself. Maybe you actually have a more reliable anastomosis. That is not proven. But this is a brick in a wall of less invasive surgery in general and both minimal access surgery and off-pump surgery. The reasons for that are the following: The reason that minimal access surgery is so limited is the most difficult thing to do through a little incision is to sew. If minimal access surgery is every going to get any place, this is a necessary brick in the wall to move that along.

Similarly, you can argue whether there is a benefit to off-pump surgery or not. The preponderance of evidence would seem to indicate that there is. But it is stuck at 25 percent of CABG in the United States. Why? Because most surgeons aren't comfortable putting the heart on end for 20 minutes to sew on a beating heart. The

potential benefit of an anastomotic device, if proved to be safe and efficacious, is immediately catalyzing off-pump surgery. If it takes a minute to do the anastomosis most surgeons are going to feel comfortable with that.

So, I think the ultimate benefit is that it is a potentially more reliable anastomosis, not clamping the aorta, not having neurological events but ultimately what it allows this whole field to progress to is that it is not going to be the same operation as for the last fifty years.

DR. TRACY: Thank you. With that as a jumping point and trying to go along a little bit with the lines Mitch indicated, we have heard the historic comparison to CABG and anastomosis as sort of the gold standard. Is that the right gold standard or is this technique different enough that we don't use sutured CABG anastomoses as the gold standard? Dr. Aziz?

DR. AZIZ: Just before answering that question, you know, we have a technique which is very safe. It is not perfect; the vein grafts may not last long but I think that is usually related to vein biology. So, I mean, we have a certain standard and if we are going to adapt a new

technology I think at a minimum it can't be worse than what we have, and I think we have to be careful on that. I think we need to sort of keep that in the back of our mind. For example, this particular device that was presented, the St. Jude device--clearly, the results are worse than what we have with hand-sewn. So, I think, you know, we have to make sure that whatever we do is not worse than what we have. It is not like we are in a void.

Regarding the sort of controls, as someone else had also mentioned, using the same patient as his own control would obviate the need to have randomized studies in the sense of, you know, having two different groups of patients. You could do one anastomosis with one of these techniques either for the distal or proximal and one doing it the old-fashioned way or the regular way with a suture technique. When you evaluate by angiogram, that in itself could be its own control.

DR. FERGUSON: I have kind of done a 180 on this because I was impressed with--I think it was Bob Emery but others too. I came in with the idea that using the traditional statistics for a control, matched control would be a good thing to

do. But the more I have listened today, the more I think that the patient population has changed so much in the last twenty years that those historical controls are truly historical and probably not relevant to what is going on today given the kinds of patients that are being operated on today, and so forth. I think, Bob, you mentioned something about that too. So, I would only comment that if we truly need control for experimental devices, then I think that we need to make those controls modern-day standard heart/lung operations.

DR. TRACY: Dr. Blumenstein?

DR. BLUMENSTEIN: I am really seconding what you are saying and maybe stating a little more explicitly that I don't see we can do anything by randomize in some sense. I think that you have to have the power of randomization to give you the stochastic equivalence between those treated with the experimental intervention and some kind of a control group. Whether it is matched or whether it is a two-group study, and so forth, will have to be discussed but there are just too many extraneous factors that cannot be controlled. I am just blown away by the number of them. So, you have to have randomization to control the experimental

intervention and let those other factors be stochastically controlled with randomization.

DR. EDMUNDS: Just to maybe start a little bit of discussion on this issue because this really is the heart of the issue, let's just look at the problems of a non-randomized control group and what are the alternatives. Well, propensity matching and univariate and multivariate logistic regression. But a lot of the technical problems are not things that we collect data on, as Bob Emery has brought out. Yet, they are very relevant to the success or failure of patency, let's say, and that will confound any kind of propensity matched control group or taking it out of a logistic regression equation because you don't have the data in there in the first place. So, I can't think of a control group other than a concurrent prospective, randomized control. Maybe somebody else can but I can't.

DR. TRACY: Mitch?

DR. KRUCOFF: Because of the breadth of range we are looking at, we really do have to be careful about babies and bath water. I think if we take this as a new device, then a characteristic first question would be is it safe? The first

in-man type of experience would be one way to go. I think we have seen at least one elegant illustration of using a patient as their own control where you have even numbers of grafts that can be characterized and randomized and carefully followed angiographically.

That is living in the morphologic side of are we hurting people anatomically by putting these things in. That would also be a very good opportunity for a bunch of smart surgeons to look at what are the technical features that we would want to capture in a larger, more definitive trial and explore that a little bit in a small but very intensively designed study. I think the one feature there that certainly stood out for me out of this morning's presentations is the potential to use a patient as their own control over a series of non-LAD grafts.

I think as you move into a more definitive "okay, this thing is safe," now is it effective, and is it effective for what? Is it effective as a stepping stone toward fully robotic surgery, or is it effective to not have to cross-clamp the aorta in 80 year-old people with crunchy aortas? I mean, it depends on the question which the FDA is very

particular about; it depends on the label; it depends on the indication.

But I think if we do this in steps there are points where patients can serve as their own control, where historical descriptors may be useful, and then I think ultimately there is a point where you are going to have to do real meaningful and probably randomized trials to show that it is effective, building along the way.

DR. HAUSEN: Bernard Hausen, Cardica. What is the worry, Dr. Ferguson? That we are over- or underestimating with our historic controls the true incidence of occlusions?

DR. FERGUSON: It is a different patient population. That is my point. We had this problem yesterday a little bit about using a group of patients that are 20, 25 years out as our control group. I don't think we can do that. Somehow or other, we have to have concurrent. Now, how that is done is up for grabs here I think. Go ahead.

DR. HAUSEN: Let's say Dr. Frater is right and patients are getting sicker; they are definitely getting older; the veins are getting poorer and all this will result into poorer outcome of vein grafts. You could hypothesize that

nowadays, if I did a brand-new control group with vein grafts hand-sewn, my results would be worse than what Dr. Mack presented to us.

DR. TRACY: I think that you are right but the problem is that we don't have a proximal control here. We don't have something that we can look at that we feel is comparable.

DR. HAUSEN: I understand that but if you are worried that when I am comparing my average patency of a device to a control, the worry would be that it gets approved because it is statistically not worse or similar to control where my control would underestimate the true prevalence of occlusions. I don't think that is the real world.

DR. FERGUSON: That is not a definition of a control in my world.

DR. HAUSEN: I know. I know, but from a regulatory point of view you are trying to prevent products, or the FDA is trying to prevent products from getting onto the market that look better than they really are and that pose a patient risk. So, if you have a control group that is worse than what the real world is showing us right now--

DR. BRIDGES: Can I interrupt? I think we

got the point. I think part of the problem here though is that one of the safeguards of a randomized trial, or at least a prospective trial--I mean, yes, perhaps the patients today are "worse" than the patients were then but what is to prevent someone from doing a study where they are selecting patients from today who aren't worse and applying the technology selectively to groups of patients who are not worse than some group of historical controls? That is the whole reason why prospective trials--it is just to mitigate against that kind of deficiency.

So, to simply stand up and say, well, you know, the patients that we are operating on today are worse than they were before, therefore, we don't need prospective trials I think is overly simplistic.

DR. TRACY: Dr. Sapirstein?

DR. SAPIRSTEIN: Given the template or the sample I provided where we use a 95 percent point estimate of patency and a lower confidence limit of 5 percent, 95 percent lower confidence limit of 90 percent, how much better can you do on a randomized control? The only reason I bring this up is because of the sample size that you would require

and the difficulty of subjecting patients to angiography.

DR. KRUCOFF: Come on, Ralph, how are you not going to submit patients to angiography? In this status of a new device how are you going to avoid doing angiograms in these patients? You are going to have to do angiograms in these patients.

DR. SAPIRSTEIN: Yes, I think so. I think that you have to do angiography on a new device but on standard procedure, a LIMA to LAD, are you justified in doing an angiographic evaluation of the control? Maybe you are. It is a point of discussion.

DR. TRACY: Dr. Edmunds?

DR. EDMUNDS: Before you stand down, because it is very expensive to do randomized, prospective, controlled trials, you have to decide in a power analysis how much of a difference is it that you want to see, and presumably a composite primary outcome, to be meaningful, and do your power analysis on that basis. Now, if you really want to say that a one percent difference multiplied by 260 million people, not all of whom have coronary-artery disease, is what is needed, therefore, you are going to have to have a very,

very small difference, like half a percent, nobody can afford that trial.

DR. SAPIRSTEIN: Exactly.

DR. EDMUNDS: So, that power analysis and what you define as a meaningful difference is critical I think to any kind of regulation that you set up for these companies.

DR. SAPIRSTEIN: Absolutely. That is why we put up that template. With 80 percent power, a 5 percent alpha, can we do--

DR. EDMUNDS: Well, what difference?

DR. ZUCKERMAN: [Not at microphone; inaudible]... the expected observed rate for a venous study would be 95 percent with 80 percent power, alpha 5, and setting a delta of 0.05, meaning that you are projecting a lower rate--

DR. EDMUNDS: I am not sure.

DR. ZUCKERMAN: --you need 150 patients. If we expand that delta to 0.07 it could be a lower rate of 88 percent and you would only need 59 patients but perhaps the delta should be tighter [not at microphone; inaudible]...consider this approach given that for having just normal CABG patients come back for follow-up angiography, as Dr. White was alluding to, perhaps can be very

difficult.

DR. EDMUNDS: Well, the five percent difference is probably in the realm of reasonableness.

DR. TRACY: Let me be clear what we are talking about. Have we moved away from a randomized trial to a trial where we are using historic 85, 95 percent?

DR. WHITE: Can I support that?

DR. TRACY: You support moving away and using the historic CABG data?

DR. WHITE: Right. The reason I say that is that obviously I am an angioplaster so I am anti-intellectual, but the point is that I do like randomized trials and I won't argue with you that that is the best of all worlds, but I think we can gain confidence that we are doing as well or better, and we have such extensive historical data, as Dr. Mack presented to us today and other data that is available, that if the manufacturer chooses a relatively high bar for patency, it could be done as a single arm because we would be sure that they would be 90 percent or better and that would certainly meet historical controls and it would be hard to argue that they were worse than historical

controls.

If the manufacturer, on the other hand, decided that that bar was too high and they wanted a randomized, controlled trial because the control group really was going to perform at a lower rate, then I think that is a decision we ought to leave to the investigators and to the company.

DR. TRACY: Dr. Blumenstein?

DR. BLUMENSTEIN: I am not sure exactly what this represents. I assume this means a single-arm trial with a criterion of success of, say, 95 percent and precluding the possibility--it is a sort of non-inferiority situation--precluding the possibility that the outcome is truly 90 percent or worse with a 5 percent delta, or whatever.

The danger here for a company undertaking such a trial with such a high bar is that if you take that sample size of, say, 150 and you have guessed wrong about what the success rate is, then you are in trouble.

DR. WHITE: And we have been here once before when companies come back to us, missing their bar and asking us to make that exception--

DR. BLUMENSTEIN: Right.

DR. WHITE: --and it is up to us not to make that exception if they miss that bar.

DR. BLUMENSTEIN: But there are two reasons why this is a real problem. Number one is that if you had started with a lower success rate, supposing it was reasonable to do so and we all accepted that it was reasonable to do so, the sample size goes up as the base reference success rate moves closer to 0.5. So, by putting the success rate close to 1.0, then you are getting a smaller sample size than you would had you put the base rate closer to 0.5. So, by setting the bar high, which is a good thing, you are in fat anti-conservative with respect to the sample size.

DR. TRACY: Dr. Zuckerman, you look like you have something to add here.

DR. ZUCKERMAN: I just want to state that Dr. Blumenstein has correctly summarized what this trial design is trying to do, say, for a LIMA trial. We are trying to show that the new device has an observed performance rate or patency rate above 0.90. Therefore, as he was--

DR. TRACY: Dr. Zuckerman, stay near the microphone.

DR. ZUCKERMAN: --if the observed rate is

0.93 instead of 0.95 they can do a sample size calculation and it will go up. But the question is, is 0.90 the right bar for this performance goal, Dr. White.

DR. WHITE: I would be very happy. Given what we know about the historical controls for hand-sewn grafts, the meta-analysis and data that we have looked at, that if I was confident that the device could do 90 percent or better at one-year patency or six-month patency, I would feel pretty comfortable about that.

DR. KRUCOFF: How about 89? How about 88? How about 87? I mean, come on, Chris, the likelihood of creating an ambiguous data set that ultimately then would occupy all of us for a day--you know, I think we have to recognize that the likelihood for ambiguity if we court certain marginal design structures is so intense--

DR. WHITE: I don't have a problem with 89.

DR. KRUCOFF: What if they don't make their endpoint? What about that they find out that in 50 year-old women, as a retrospective subgroup, it was 100 percent? You know, the vulnerability to starting in the wrong place to then, in this venue,

having a long discussion about completely ambiguous data is huge and I think the key is don't start in the wrong place.

DR. TRACY: I think the problem that will come up is that there may be times where it would be inappropriate to have a historic control, but it may be just as inappropriate to have the patient serve as their own control--a single vessel study. There are all kinds of reasons why either one of these is going to be not optimal fit for any given device that is being tested. So, I think there has to be a little bit of breadth. I think that gets back to the idea that you cannot possibly have an exact study that has to be done by each one of these different devices because they are different devices. So, the patients that are going to be enrolled are going to be different from one study to another. I don't know how to get around that except to accept different controls in different studies.

DR. EDMUNDS: But a Type 2 error is just as bad as a Type 1 error.

DR. TRACY: Dr. Emery?

DR. EMERY: I think two issues come to mind. One is that patients serving as their own

control will likely only be utile in proximal anastomotic studies and this would separate the distals from the proximals.

The second thing is that, on the side of patients as their one control, you have to be sure you are asking the proper question from the study. For instance, there may be biology of aging. We know from prosthetic valves that a bioprosthesis in an elderly patient will last a lot longer than a bioprosthetic valve in a younger patient. The same may be true for connectors because of the biology of wound healing and inflammation. We don't know that. So patients serving as their own control would be a good means of separating out the patients at risk and the patients not at risk based on their individual biology.

In our paper published in Circulation, the younger patients that had the aggressive restenosis were at risk for the connectors. On the other hand, if you are looking at stroke risk, which has been brought up, that is not a good study for patients as their own control because, perforce, you have to put a clamp on the aorta for all patients in the study to randomize them and that is one of the highest risk things that we are trying

to avoid with connectors, particularly in the aged.

So, it is important to address the question before the study is designed to examine what answer you are looking for, the value to the patient population or the patency and effectiveness of the connector itself.

DR. BRIDGES: I have a question related to what Wolf Sapirstein said, which is that one question the panel should consider is, if we are advocating a randomized trial, how do we feel about the risk to control patients being subjected--assuming that the patient can't serve as his own control for example, how would we feel about control patients being cath'd at six months or one year?

DR. TRACY: I think that was Dr. White's point, that it is hard to get patients back. We have historic data on those patients regarding long-term patency.

DR. FERGUSON: Some of the hardest data we have seen today is from Dr. Klima, at Hanover, and they don't seem to have a problem over there when they set up a design trial for any of these issues. I am not quite sure why we do.

DR. YANCY: Well, just to take some

exception to that, any study design that comes up has to clear local IRBs that are under increasing scrutiny with regards to what they will subject particularly control individuals to. So, I think that Chris' point is not an inconsequential consideration. Certainly from the stent era we do use MACE as an endpoint and I wonder how that compromises this study design if we use MACE.

DR. TRACY: So, we have the scenario of a historic control. We know what the patency rates are. We have the scenario of the patients serving as their own control, which will limit the type of device that can be studied. There will be limits there. And, we have a scenario of a randomized, controlled study group that would be brought back for intervention. I think each of these has some problems. Dr. White?

DR. WHITE: I think that we need very hard endpoints. I think hard endpoints make for smaller, more firm studies. So, I really think we want patency. I think we know already that asymptomatic patients show up this way. We have heard that perhaps non-invasive testing isn't an adequate screen so we want the hard endpoint. If we ask for patency at whatever interval, six

months, one year, then I think we take care of Dr. Edmunds' concern about the procedural issue because if you are having closure at procedure you will see the closure at six months as well, and you can then backtrack that.

I think if you do single-arm studies with objective criteria, which has its own problems with a slippery slope, at least you can subject those patients to a hard endpoint of patency, and I think that minimizes the number of patients who are studied. It gives you the hardest endpoint for the follow-up. And, I think it really puts the patients who are at risk for this problem as the subjects of the study as opposed to the control population.

DR. TRACY: Dr. Hirshfeld?

DR. HIRSCHFELD: I think there are really two questions. The first question is do the devices perform equivalently to standard hand suturing? That, it seems to me, can be answered in a study with a relatively small population of patients and a study design analogous to what the Hanover people presented. That has a very hard endpoint and has a great deal of statistical power, and that could settle this question with a

relatively modest number of patients, I would think.

The second question is the question of what global benefit does the patient derive from this, and those are all surrogate endpoints. They are neurological endpoints and they are MACE endpoints. That could be addressed with a larger randomized trial in which all the endpoints that were collected were the surrogate endpoints in terms of perioperative neurologic events and long-term cardiovascular MACE and wouldn't really require angiographic follow-up.

So, it would seem to me that one possible approach to this issue and I think Dr. Mack's comment about the importance of continuing development in this field, independently of how the current generation devices actually sort out, is a very important point. But the issue of whether or not we are hurting patients in terms of graft patency can be answered with a relatively small trial, and then the issue of whether or not patients are deriving benefit in terms of surrogate endpoints could be answered with a larger but less complicated trial.

DR. TRACY: Dr. Blumenstein, do you have

any comments on that type of a design?

DR. BLUMENSTEIN: I am sorry, I wasn't paying attention. I am doing some trial size computations.

DR. HIRSHFELD: I am sure that if you try to do a trial size computation there is no way you can concentrate on anything else. But what I was thinking was that if you did a study design analogous to the study that was described from Hanover in which each patient serves as their own control for the performance of the device in terms of graft occlusion, that is a study that has all of the variables controlled through the randomization process and has the highest possible degree of precision in terms of the outcome event, and should be able to be completed with a relatively modest sample size.

DR. BLUMENSTEIN: That is exactly what I am trying to compute.

DR. HIRSHFELD: But that doesn't answer the other question which is are patients better off in terms of events because of the use of the device, or are they equivalently off, or are they worse off. That would require a larger trial in which patients are randomized between the device or

not the device and the endpoints are all the clinical endpoint events, neurological events and cardiac MACE.

DR. BLUMENSTEIN: Well, we can discuss this later I suppose but when designing the trial, in order to size the trial you have to pick a primary endpoint. Basically, I think what we are stuck with here in this discussion, without getting into a great amount of detail, is the dichotomous outcome or either success or failure assessed at, say, seven, eight months down the road, giving a window for six-month angiography or something like that.

The secondary endpoints or the other benefits that might accrue then have to be assessed in the context of the sample size computed for that structure of the study and within the framework of that study.

I think what you are asking is, if you were to do a two group study, then you would have a much better idea of the overall impact of the benefit of this and a two group study might be something like a treatment failure-free survival study where you are using a time-to-event endpoint and you randomize into two groups. In that case,

what you gain is that the patients in each group are assessed with respect to all the outcomes and are not muddied by having one vessel randomized to the experimental procedure and one vessel randomized to the control procedure. Maybe that is a good follow-on study, a postmarketing type study.

But it seems to me that if you can achieve the matched vessel type of study where each patient is serving as their own control. If that study is doable administratively, if you feel that you can do the quality control, implement the intervention, the randomization, etc., then I think that gets at the answer about whether there is success with respect to the vessels and a comparison to a control which would take away the host factors.

DR. SAPIRSTEIN: [Not at microphone; inaudible]...safety together with effectiveness, and much of the effectiveness of these devices has yet to be determined by virtue of facilitating other changes to the performance of CABG which haven't in themselves been determined. For instance, off-pump, beating heart, MIDCAB and all those sort of things. One of our most important considerations is patency right now. We are interested in safety and MACE events but right

now--well, not right now but at this stage of the questions we are really interested in effectiveness.

DR. TRACY: I think that is really very important because it doesn't matter how safely you can do something that doesn't work.

DR. SAPIRSTEIN: That is right.

DR. TRACY: So, I think that a definition or determination of patency is critical to this.

DR. HIRSHFELD: To put this in context, we have a currently approved, marketed device about which some data has surfaced that raises the question that its performance may actually be inferior to conventional techniques. The data to date are inconclusive but there is enough of a cloud that that question has arisen. So, I think our first obligation is to answer the question as to whether or not it is equivalent or not to conventional hand-suturing techniques. That, I think, is something that can be answered with a highly focused trial. Because if it turns out that it is inferior, then all the other questions, all of a sudden, are moved way to the background. If the trial can demonstrate that it is equivalent or superior to conventional techniques, then the next

question arises which is, well, does that benefit in performance translate into clinical outcomes.

DR. TRACY: Dr. Maisel?

DR. MAISEL: In my view, I don't think that one size fits all. I think there is more than one way that we could feel comfortable with the efficacy, and certainly a randomized clinical trial would meet that standard. But I certainly can imagine an observational trial with 10,000 patients and no events or, you know, 1,000 patients and 5 events. There certainly could be an observational trial, a one-arm trial that I think would meet that standard. So, you know, the challenge of drawing a line in the sand is a big challenge but I don't think it is impossible.

DR. TRACY: Dr. Yancy?

DR. YANCY: This is tangential and I am happy to table this item at the Chair's prerogative, but Dr. Hirshfeld's reference resonates clearly with the concern that has been building in my mind over the last several hours, and that is that there is a device on the market about which questions have been raised. Part of the questions perhaps have to do with the umbrella under which it received approval. Part of the

questions may have to do with the very issue we are discussing right now in terms of trial design. It is hard to know the denominator. We know there are a number of events that have come to the FDA.

It is also incumbent upon us to support the development of the minimally invasive surgical procedures. So, I think the analogy of babies and bath water is correct. But I am beginning to wonder if it is anywhere within our purview to address this one specific device, or maybe it has to be set aside to another entity, but it seems as if it is not unprecedented to make statements about concerns regarding the safety of a device that is already marketed, not necessarily to withdraw it but indicate that we have seen a signal that raises questions. I am not saying it is a bad device because, again, the statistics of looking at this are difficult. If this is inappropriate, then I will withdraw this and beg apology, but it is a question that I would like to pursue.

DR. TRACY: If we could let the FDA speak to that.

MS. FLEISHER: Dina Fleisher, from the FDA. This issue has been addressed by the FDA. There was a whole team here from our Office of

Surveillance that has been taking care of this and addressing it in the purview of the limits that we have at FDA. For the interest of this panel meeting, that really isn't probably relevant to this particular discussion of what future designs we would like to have.

DR. YANCY: One follow-up question?

DR. TRACY: Yes?

DR. YANCY: Are there activities you plan to do, without compromising your deliberations, that you can tell us? I mean, is there a time sequence or is there a statement to be prepared? Is there anything that you can say in that regard or is that an inappropriate question?

MS. FLEISHER: We could probably do a one-minute summary if that is helpful to you.

DR. YANCY: I am happy to do that off-line since I may be the only person who has this concern.

[Several members reply, "no, you're not."]

Then I think it would be important to us.

MS. FLEISHER: I will let the lead reviewer from that office actually address that.

MS. HOANG: I am Quynh Hoang, from the Office of Surveillance and Biometrics. As Dina

Fleisher has indicated, the FDA is aware of a number of MDR reports regarding the Symmetry device and we have convened a committee, a cross-center committee, to look at the issue. Your question is specific to what FDA plans to do about the adverse events that we have seen with the Symmetry, and the only thing I can say is that we are working with the company.

DR. TRACY: Thank you. Dr. Slaughter?

DR. SLAUGHTER: Dr. Slaughter. Just two issues, using a patient as their own control and trying to identify two arteries has been done before, and that was the ARIA trial using a synthetic conduit. Although it seems appealing, it is extremely difficult to administer. The issue that comes up is that even preoperatively you can identify two vessels that you think are similar. The problem is you are doing that on a preoperative angiogram for which the stenosis may be different in each, and the question is were they under-filled because the dye is not getting there or are they really that small? So, you are really using a very crude comparison of external diameter. Then, when you get there you sort of flip a coin and pick one. You open it; you can size it; you open the other

one and it turns out it is different.

The other issue is still that although they may look the same size, you know, before you start there are other issues as to the size of the bed they supply and things like that. It becomes very difficult technically to administer and it can prolong the operation significantly when you are trying to randomize them intraoperatively. So, although it seems appealing, and certainly to use the patient as their own control just in general, and if you do complete angiography as opposed to selective angiography it is more doable, but to truly try and randomize two what you think are matched vessels in an individual patient is technically very difficult.

DR. BRIDGES: I don't think you need to necessarily match the vessels in each patient. I think that the randomization will take care of that. I mean, you don't match patients that are randomized. You don't say, well, I am going to randomize these two patients and I think they are equivalent. The randomization itself--it could very well be that the first patient will have one OM that has a tight stenosis and one that doesn't and then in the next patient the converse will be

true. So, as long as you are randomizing the technique that you use within the patients as you go along, that should be a valid study design, unless I am missing something.

DR. SLAUGHTER: Then you are back to where you have a control that is not getting the device and you have to have follow-up with invasive monitoring and you are subjecting a control to an invasive test.

DR. BRIDGES: No, what I am suggesting is the same design that the group in Hanover used. In that case, unless I misunderstood it, each patient either had two or four anastomoses performed. If they had two, then a random decision was made as to which of those two would be done with one technique, hand-sewn versus the device and each patient was randomized in that fashion so that there was no control group that was angiogrammed. These are all patients who had an anastomotic device used that served as their own control. So, within those patients it is not relevant whether the two arteries that were randomized were equivalent. That is not the question.

DR. SLAUGHTER: I understand. I think they are close but I think it does make a

difference because there is a difference in distals. Unless you quantify the information when you start to review it, it is very difficult to assess patency.

DR. BRIDGES: Sure.

DR. EDMUNDS: Well, to show off the culture at the University of Pennsylvania, I am going to disagree with my colleague, Dr. Bridges, and agree with Dr. Slaughter. There is plenty of data to show that the degree of proximal stenosis in a native artery influences patency. Moreover, there is a difference in patency rate between target arteries--circumflex, right, LAD--well, LAD is not in this equation. And, it will be a logistic nightmare, Charles, to try to get patients in which you can randomize the arteries. You just won't be able to get enough patients without getting into a whole lot of institutions, I don't think.

DR. BRIDGES: Sure. I am not trying to say it would be easy or simple to interpret, but I am simply making the point that I think what has been suggested is following the design of the Hanover study and, as I understand it, that is the way they conducted the study and that is my point.

My point is to say that their study did not involve trying to match arteries. They simply randomized technique selection within patients who had an even number of arteries. I certainly acknowledge that that is not the same question as to whether the degree of stenosis or the circumflex versus the LAD, or whatever, will have different patency rates. Hopefully, that would be taken care of by enrolling enough patients but there still would be challenges with that kind of a study. I am not advocating it; I am simply trying to confirm what the design of that study was.

DR. TRACY: I am going to try and move us on to some of the next points, but just to briefly summarize, the clear message is that not having some type of control or some comparative basis is not acceptable. Just having a study where the device alone is being analyzed and then hoping that something will be picked up at a later point is not an adequate endpoint. There needs to be some type of control built into the study but we are having a hard time grappling with what that control should be. Should it be intra-patient; should it be patient-to-patient; or should be looking at a hard outcome compared to historic control, patency

outcome compared to historic control plus randomization on surrogate endpoints such as neurologic events.

I think that we would need, and I don't think we can do that sitting here, a statistical analysis to figure out what size would be needed for each of these different models--unless he is very good and very fast. I would like to move on to some of the other issues and maybe, when Dr. Blumenstein is read, to come back to that if we can.

DR. KRUCOFF: Cindy, just before you leave that, let me make one comment about size. The other side of what we have heard a lot of wisdom on today is that you can drive the density of endpoints into a higher direction to do a smaller trial. So, if you know that actually arteries that have greater plaque burden are more likely to fail, or if you have diabetics they are more likely to have problems, you can use propensity scores to actually target a higher risk population and do a smaller trial. So, you get into the conundrum of you have to find those patients--

DR. TRACY: I think we have had some disagreement that a propensity score would be

effective in comparing at least to historic controls so--

DR. KRUCOFF: I am not talking about historic controls. I am talking about how frequently you can anticipate a failure endpoint in a population to do a prospective study and do 100 patients and have an answer rather than 500 or 1,000 and have an answer.

DR. TRACY: Right. Well, we will leave it there for the moment. Let us know when you have finished your analysis, Dr. Blumenstein.

The second set of questions, with regard to device placement and device design, please address the following: Given the considerable differences between the proximal and distal CABG anastomoses, what, if any, differences in study criteria should be required?

My observation would be you can't do a proximal without doing a distal. I am not clear, Dr. Sapirstein, on exactly what the question is here.

DR. SAPIRSTEIN: There has been a lot of discussion about the connector device which is strictly for the proximal anastomosis of a venous conduit to the aorta and doesn't involve anything

about suturing to the distal coronary. Now, there are a lot of devices which specifically address the distal anastomosis to the coronary artery and not to the aorta, and other devices which are just going to anastomose an artery, the LIMA to the LAD or something of that nature. So, there is a lot of variation in the indications for a participant device.

DR. WHITE: Well, I would say that the first criteria, the primary criteria has to be patency, and patency whether it is proximal or distal doesn't matter to me. I want to know that the graft and the device is patent and I am not confident that we have non-invasive ways to screen these patients for patency. So, that brings us back to a hard endpoint, patency. So, I am in favor of applying the same criteria to the distal as I would to the proximal anastomosis.

DR. TRACY: John?

DR. HIRSHFELD: I am saying this with some fear that I will subsequently be exposed as being simplistic, but I think that the issues are the same and I think that the trial design, whether we are examining proximal or distal anastomoses, should be able to be the same, with the same

departments.

DR. WHITE: No, they are not the same.

DR. HIRSHFELD: Okay, I knew somebody would bring that up.

DR. TRACY: Dr. Edmunds, do you want to make some comments?

DR. EDMUNDS: I would suggest for starters that for proximal saphenous vein, aortal saphenous vein anastomosis the following for endpoints: An aortic complication, changes in neurocognitive state or stroke, patency whether it is an occlusion or stenosis, hemorrhage, and acute revision, you do it at the table or just after you closed, and any device-related death as endpoints. I have left out myocardial infarction.

DR. TRACY: I think those were the reasons for wanting the MIDCAB in the first place, to reduce some of those neurologic types of outcomes. The one thing that is in there though that is similar to distal would be patency. But I agree, those are additional concerns for the proximal anastomosis. Dr. Ferguson?

DR. FERGUSON: I think we can have the same endpoints but the devices themselves are so dissimilar and used for such different reasons that

we have to be cognizant of that.

DR. KRUCOFF: I agree with Tom. I think it has been made very clear that even the technique of putting something into a beating heart where you are doing a distal anastomosis may be totally different than the technique of connecting something to an aorta. There may be some overlap in the endpoints but these are separate trials.

DR. SAPIRSTEIN: A question that comes up, Hank, is, for instance, do you require a six-month patency evaluation for a proximal and a six-month for a distal, or would you require different rigor of evaluation for a proximal, which is a large vessel, a large anastomosis, relatively crude? That is one of the questions that sort of distinguishes the two areas.

DR. EDMUNDS: Wolf, I am going to defer to the collective wisdom in the room.

DR. AZIZ: From the data that we saw with the other device, by six months we were seeing problems so I think even though the time period may be different I think six months should be at least the minimum time frame.

DR. TRACY: Dr. Kato?

DR. KATO: I would agree with Dr. Aziz

that six months should determine patency both for proximal and distal anastomoses. The only difference with the distal is that the criteria of any aortic complication or stroke won't be there.

DR. TRACY: Dr. Yancy?

DR. YANCY: Going back to the question of being simple, I think simple is good, John, and the study design is quite similar, in my judgment. It is just the endpoints and surrogates and the variables that we follow are different, some referable to the aortic anastomosis, others referable to the technical concerns. But ultimately the study designs are not terribly different. It is just the length of follow-up and what we follow.

DR. TRACY: Yes?

PROF. KLIMA: Uwe Klima, from Hanover. I think the myocardium does not care whether the blood flows through a proximal anastomotic device or through a distal device anastomotic device so the endpoint really should be patency rate after six months and does the anastomosis look good whether it is running through a proximal or through a distal anastomosis.

DR. TRACY: Dr. Weinberger?

DR. WEINBERGER: Yes, I am sitting here and I am wondering whether people are beginning to blur the difference between graft patency and graft stenosis. I think that the numbers that people are talking about, looking at six months, makes sense in the context of stenosis. If you are talking about patency, the numbers sound to me like looking just at six months you are not going to have enough events. Maybe we can get the surgeons to comment on that. You care ultimately about how the graft feels when it has done healing. The failure rates that we are talking about really are complete occlusions. If you look at six months, is the acute response to the surgical process, given these new connectors, completely finished by that point?

DR. AZIZ: You may not get complete adhesion but you may even get severe stenosis so even that is bad.

DR. WEINBERGER: I agree that it is bad, but we are talking about endpoints being graft failure. Is that right?

DR. EDMUNDS: Well, let's just stay with the aortic saphenous vein proximal anastomosis and then deal separately with distal. Okay? The reason is that I think that you can't say when

healing ends, except when you change your address permanently. So, I think you just pick a period in time and you say that is our endpoint. If we see 25 percent stenosis in 50 percent of the device applications and we see 3 percent stenosis in the control group, that probably would work out, if we got enough power, to significance. Now, how important that is, that is not the question. That is not the outcome either. It is the stenosis. That is what I am advocating.

DR. WEINBERGER: So, just to concretize this, we are talking about a continuous variable at six months and we are talking about not measuring graft patency rate, although that might be a secondary endpoint. We are talking about the difference in the distribution of patients with respect how tight the stenosis is proximally. Is that right?

DR. EDMUNDS: The question you are asking is the same as what is the patency rate of the rapamycin stent at five years? No one knows. We haven't been five years. It could be 50 percent.

DR. TRACY: So, I guess the answer here is that you find a time, a period of time where you look and that becomes the data point that you have.

DR. KRUCOFF: Well, there is an issue with a biomarker. In fact, what you are describing is minimal luminal diameter so as a continuous variable you take your point, six months for the proximal anastomosis in the device group. The minimal luminal diameter is smaller than for the non-device group. That may be a statistically significant difference. Then a separate question becomes is it so small that they are having angina, infarctions or deaths? And, that is a trial design that is, again, pretty well established but it is a biomarker where the statistical significant difference is not one and the same as the clinically meaningful endpoint.

DR. TRACY: Let me skip ahead to part b), are there certain aspects of the clinical study design, example, length of follow-up and endpoints, that should be required for all devices irrespective of device form and function? for example, the U-clip performance closely duplicates that of a suture, whereas the Symmetry has greater similarity to a stent.

So, where we are I believe is that there would be specific aspects of a clinical trial design that would be different whether you are

talking about proximal or distal, but there has to be some concrete endpoint, and probably you could come up with a generic time frame--six months, nine months, whatever you choose--whereby the patency or the percent stenosis would be analyzed. The other endpoints might be more appropriately analyzed, of course, at different times--neurologic events acutely or catastrophic events, obviously, would be analyzed acutely.

DR. BRIDGES: I think to answer this question, 2.b, my opinion would be that these devices are so different and so protean in their designs that I think it would be difficult for us to prospectively or a priori try to figure out what we expect the differences to be. So, I would think that the design of a study for all distal devices ought to be the same, at least as a starting point. I mean, you might look at a device and say, well, that looks like a suture and, therefore, we don't need maybe as large a study group. But I think the most straightforward approach would be to have the same endpoint irrespective of what our opinion about how we think the device will function is.

DR. KATO: But the implication really is, is one device similar to another one, which is a

discussion, as Dr. Frater who I guess is not here anymore brought up before about, you know, is this device definitely going to be a PMA or is it going to be a 510(k)?

DR. TRACY: It is not in the purview of this group to change whether something is a 510(k) or PMA. That is completely off the table even as a question to this group. The question really is study design. I think that you have to design a study that is going to capture important endpoints with it is a 510(k), PMA, or whatever you call it. A concrete point in time to say let's look and see what the anatomy looks like, with it is a continuous variable like stenosis or absolute patency/occlusion, that is a time you choose that makes biologically some sense--six months, nine months, and the other variables appropriate to those types of outcomes. Does that seem to make sense?

DR. YANCY: So, in that context I would like to support what Dr. Bridges said, that there is sufficient variability and sufficient degree of unknown that the answer to the proposed question is that there should be some consistency in the time of follow-up--

DR. TRACY: Right.

DR. YANCY: --irrespective of the mechanism of action.

DR. TRACY: Right. I think that is a good point. Part c) to that question, it is rarely possible to determine the cause of conduit failure. Can you suggest criteria to determine whether a failure is device related? Dr. Yancy?

DR. YANCY: That is the essence of a clinical trial design. You have to have a clinical trial that rules out the confounders, or at least equilibrates them between the intervention and reference group so that you can have only one remaining variable and presume that it is, in fact, the device. I mean, that is the whole purpose for a clinical trial.

DR. ZUCKERMAN: That is perhaps the first part of the equation, but FDA was also wondering whether the panel agreed with some of Dr. Krucoff's earlier comments. For example, should some of the methodologies from the stent trials be adapted to these CABG trials, meaning should there be an independent clinical events committee looking at these events to try to determine cause of graft failure. Two, is it worthwhile to, for example,

have an independent core angiographic laboratory look at the angiograms, at least in a percentage of patients, to confirm what the sites are calling device versus non-device related?

DR. EDMUNDS: Bram, do you have the criteria for the stent trial? I am not sure that I know what those were.

DR. ZUCKERMAN: A set of criteria has been developed over the last ten years in order to minimize potential sources of bias and to make sure that we are comparing apples with apples, and they include randomization, use of an independent clinical events committee and, because of the importance of correct angiographic analysis and the known ability of site investigators to look at angiograms and develop measurements that can't be confirmed, the use of independent core labs. Those are the main ones.

DR. MAISEL: I think an independent core lab is obviously going to be a critical part of any assessment of graft stenosis. I do think that an independent data and safety monitoring board or clinical events committee is also a critical component. I think getting at the issue of cause of device failure or cause of failure of graft

patency, whether it is due to the device or not, is going to be extremely difficult based on angiographic or clinical criteria, and I think, you know, the trial designs we talked about are really the only way to get at that.

DR. AZIZ: I think the cause of graft patency or failure sometimes may be clear-cut. For example, if you are doing an angiogram and you see 90 percent stenosis at the proximal end, that may be okay but if you do the angiogram at six months and the graft was stenosing at three months and the flow was slowing by six months, it may be occluded. So, you know, I don't think it will always be clear-cut but sometimes I think it will be but sometimes it may not be. All you would say is that the graft is occluded and you may not be able to say if it was, let's say, a rheology type problem or whether it was because of stenosis. So, hopefully, by doing a randomized study that might, you know, become clearer.

DR. KATO: But one question for you, from what I hear from the angiographers, when you get stenosis or an occlusion from one of these devices, the clot or the platelets go right up to the edge of the aortal-vein junction. Correct? Because

that is relatively atypical for a hand-sewn graft with a good cobra head which is usually open and then there is clot distal to that, which suggests that it is not a proximal anastomosis problem.

DR. WHITE: I think that when you close a graft--I was interested in some of the images that were shown today, and I think John was too, about some of the stenoses in the middle of the graft. What I think you are saying is that you don't know if it is intimal hyperplasia from within the stent part of the device or whether it is the middle part of the graft that actually goes down because as soon as the graft goes, then the thrombus propagates. In the hand-sewn stuff you have to make that hood and we always have a little nipple. These devices seem to go right up flush. But I don't know if you can tell where the problem started angiographically after the occlusion has occurred. It could be with the device or it could be in the middle of the graft.

DR. KATO: But don't you think if the clot or the platelet plug goes right up to the end of the graft, you know, to occlude the device that most likely that is where it started? In the standard hand-sewn anastomosis--you are right, you

still have that little nipple there.

DR. TRACY: Are we struggling with the fact, exactly what the FDA is saying, that it is difficult to determine the cause of conduit failure? I am not sure that anything we have discussed so far has really gotten us any closer, except to say that having an independent DSMB and core lab to look at it. I am not sure what they are looking at though. I mean, we don't understand the pathology, as far as I am hearing from this discussion. Unless, Dr. Emery, you have something that would clarify this.

DR. EMERY: I don't think so. I agree that when you get either a proximal or distal stenosis, thrombosis propagates to the next major branching which in vein grafts is either the proximal or distal anastomosis.

What I was going to address here was the issue of distal anastomoses because you need to remember that the conduits are different. Of all the data we have seen today that is variable, the data that is least and almost invariable is the early and one-year patency of internal mammary artery grafts. As Michael Mack has said, we need to think like cardiologists where we solve problems

rather than fight about them. The problem of the LIMA to the LAD is fairly straightforward.

Historical data is new. It is done on MIDCAB and done on off-pump surgeries. There are multiple papers and very recent literature and it is very solid data, and you are evaluating an artery to an artery anastomosis with a stent-like--I don't want to say a stent, a stent-like process there so interventional angiography could be applied to a mammary to the LAD. In saphenous vein grafts that is not true because the conduit is variable for various individuals. So the criteria for establishing patency leans more towards randomization and, as Dr. Edmunds has addressed, there are different patencies for different systems, different run-offs and different degrees of stenosis with the vein graft in particular. That does not appear to be true with mammary artery grafts. So, you may have to vary your study criteria for the conduit that is being utilized in a particular study.

DR. TRACY: John?

DR. HIRSHFELD: Thinking ahead to what the data will be, the first endpoint is going to be patent versus not patent and that is going to tell

us whether there is a performance difference between the device and the traditional technique. Patent versus not patent is not going to say anything about the etiology of the loss of patency. There likely will be a group of grafts that are patent but stenotic and in those grafts the location of the stenosis will probably give us some insight as to what the etiology of the impending failure of that graft would be, and we would probably be able to tease out the answer to the etiology of increased overall graft failure from that data.

DR. TRACY: So, it really becomes observational, once again emphasizing the need to have angiographic follow-up so we can over time figure out what these failures are related to. Dr. Yancy?

DR. YANCY: I think there is just one other variable referable to the question that Dr. Zuckerman has on the table that captures everything we have been dealing with. The one concept we haven't addressed is that of bias. There is no way that this can be a blinded protocol because the surgeon knows what he or she has done. And one of the strengths of having adjudication committees,

DSMBs and core labs is that it really mitigates that whole variable. So, I think the answer to what you have raised, Bram, is an emphatic yes, we do need to populate that study with the usual complement of oversight committees, maybe even more so because of concerns we might have.

DR. BRIDGES: I agree with that and the point that Dr. Hirshfeld made. I think it might be important to make sure as we go through this evaluation process that some attention is paid not just to patency versus non-patency, stenosis versus non-stenosis, but that a deliberate attempt be made to indicate the distribution of stenoses within grafts and that might provide additional useful information. I mean, typically that information is not available when we read studies of this nature but, you know, if you found a different distribution of stenoses that might provide the clues as to whether it was device related.

DR. WHITE: I would like to say that I think we can fulfill two out of three of Bram's criteria, that is the core objective criteria, the core lab and DSMB. I would still like to leave the door open for a trial that is a single-arm objective performance criteria trial. That would

still lend itself to DSMB oversight, high rate of angiographic follow-up and independent assessment of the angiographic endpoints, and worry about the slippery slope issues that are real that will come up if you come close but don't make the endpoint.

DR. SAPIRSTEIN: We have used the generally applied criteria for conduit patency as greater than 50 percent, not more than 50 percent stenosis. If there is stenosis greater than 50 percent, we have considered that an obstructive lesion, a failure. Is this an acceptable endpoint?

DR. FERGUSON: I am no angiographer by a long shot, but I think we know from the rheology that 50 percent is a flow-limiting lesion--

DR. SAPIRSTEIN: Yes.

DR. FERGUSON: --so I think that is a good place to start.

DR. WHITE: I would like to start at the place where intervention is contemplated, and I think that failure would be defined as the level at which you would be willing to reintervene either with reoperation, angioplasty or stent. I think that either 50 or 70 percent is going to be that threshold.

DR. KRUCOFF: I think as a true continuous